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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/702,134	10/31/2000	Andrey A. Boukharov	04983.0201.00US00/38-21(5	8935

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/702,134	BOUKHAROV ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1* is/are allowed.

6)☒ Claim(s) *8-11* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 10, 2007. Currently, claims 1, 8-12 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. Any objections and rejections not reiterated below are hereby withdrawn.

a. The 101 rejection previously of record has been withdrawn in view of the new evidence provided by the examiner.

The examiner carefully considered the arguments that applicants believed SEQ ID NO: 7212 comprises a Gibberellin based upon homology and Table 2 at positions 29572-30174. The examiner performed extensive search of encoded proteins of Gibberellin C-20 and found over 13 additional Gibberellin known in the art at the time the invention was made. An alignment of the known Gibberellin is provided in Kang et al. (Plant Physiology, Vol. 121, page 373-382, October 1999). A comparison of the encoded protein from positions 28575-30173 of SEQ ID NO: 7212 with the prior art illustrates the conserved regions of the enzyme. The sequences do differ in the region of amino acid 106-116. The amino acid from SEQ ID NO: 7212 would produce a protein comprising RAQRRAGESCGY. The amino acid from the art would produce RRSGARGRTAY. The regions that differ do not appear to be within critical domains, according to Kang. The R, G, GY appear to be conserved over the art, see Kang. Similarly, Perez-Flores (J. of Experimental Botany, Vol. 54, No. 390, pages 2071-2079, September 2003) aligns 7 Gibberellin molecules and the region where the variations between SEQ ID NO: 7212 exist do not appear to be in critical regions. Therefore,

given the high degree of similarly between SEQ ID NO: 7212 and Genbank U50333, a Oryza sativa gibberellin C-20 oxidase mRNA and the alignments taught in the art to demonstrate the encoded protein does not differ in regions which would likely affect the activity of the enzyme, it is more likely than not that positions 28575-30173 of SEQ ID NO: 7212 encodes a gibberellin C-20 oxidase. Thus, the entire SEQ ID NO: 7212 would have at least one use to meet the utility requirement under 101.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to nucleic acid molecules sharing between 90-100% identity with SEQ ID NO: 7212.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

An alignment of the known Gibberellin is provided in Kang et al. (Plant Physiology, Vol. 121, page 373-382, October 1999).

Similarly, Perez-Flores (J. of Experimental Botany, Vol. 54, No. 390, pages 2071-2079, September 2003) aligns 7 Gibberellin molecules.

Guidance in the Specification.

The specification provides no evidence that variation up to 90% over SEQ ID NO: 7212 would maintain the use of gibberelin C-20 oxidase. The specification teaches SEQ ID NO: 7212. The specification provides, in Table 2, a very basic outline of the possible components of SEQ ID NO: 7212. The majority of the regions identified are not characterized. From position 28572-30174, Table 2 suggests the region is "probable gibberellin C-20 oxidase". The specification fails to provide any guidance regarding molecules that have variation.

A nucleic acid with 90% identity with SEQ ID NO: 7212 would be permitted to have 6,900 differences over the sequence. A nucleic acid with 99% identity would be permitted to have 690 differences over the sequence.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to enable the skilled artsian to use the claimed invention. The teachings of the specification and of the prior art do not enable one skilled in the art to use molecules sharing between 90-99% sequence identity with SEQ ID NO: 7212. Thus, the claims as written encompass allelic and splice variants SEQ ID NO: 7212 and fragments thereof, naturally and non-naturally occurring mutants of these sequence, variants isolated from other organisms, etc. In the approximately 69,000 bases of SEQ ID NO: 7212, a sequence which is 90% identical would encompass a sequence with 6,900 differences. The specification has not disclosed a biological function for the large genus of molecules encompassed by the claims, or otherwise provided guidance with respect to how such molecules may be used.

With respect to the claims requiring percentage identity, it would be unpredictable for the skilled artisan to determine how to use the nucleic acid sequence which shares

homology with the claimed sequence. The response asserts that SEQ ID NO: 7212 comprises known nucleic acids which encode proteins, however, in the event that the variation exists in these regions, the nucleic acid would not share structure with the asserted use. For example, the region of 28575-30173 of SEQ ID NO: 72 upon which applicant relies up for utility is only 1571 nucleotides in length. In the event that the variation provided by the claims existed in the region which applicants provide is the useful part, the skilled artisan would be unable to use the claimed invention. For example, if the 1571 nucleotides of the gibberellin C-20 oxidase were altered, the nucleic acid would be unable to function as gibberellin C-20 oxidase. Thus, the nucleic acid of the claims would fail to be useful as a gibberellin C-20 oxidase. The skilled artisan would be required to perform unpredictable and undue experimentation to determine how to use nucleic acids which share only a percent identity with the claimed nucleic acid. With respect to 99% specifically. 99% permits up to 690 variations in the sequence of SEQ ID NO: 7212. This would permit changes in half of the residues of the gibberellin C-20 oxidase including those residues that materially affect the function of the enzyme. It would require further experimentation and trial and error research to determine how to use the sequences which are similar to those provided by SEQ ID NO: 7212.

Accordingly, while one of skill in the art could conduct further experimentation aimed at, e.g., identifying a particular function for the molecules of the claims, such a function is not presently known, and the outcome of such experimentation cannot be predicted. Thus, it would require undue experimentation to use the claimed invention.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art for determining the function of nucleic acids, it is unpredictable how to use sequences that differ at any number of locations and affection the function of the nucleic acid. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The analysis used in this Written Description rejection follows the guidelines provided in the Federal Register, Vol. 66, No. 4, January 1, 2001, beginning at page 1099 (referred to in the rejection as "the guidelines.").

The guidelines direct one, for each claim, to determine **what the claim as a whole covers** (p. 1105, 2nd column).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a

nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA…' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Claims 8-11 encompass molecules that are 90%-100% identical to SEQ ID NO: 7212, and which also may be flanked by sequences of any length and identity. Thus, the claims as written encompass allelic and splice variants SEQ ID NO: 7212 and fragments thereof, naturally and non-naturally occurring mutants of these sequence, variants isolated from other organisms, etc. However, the specification does not exemplify nucleic acids that have 90-99% identity with SEQ ID NO: 7212. As a result, the claims read on additional variants, mutants, homologues, etc., that differ completely from SEQ ID NO: 7212 with respect to both structure and function. A nucleic acid with 90% identity with SEQ ID NO: 7212 would be permitted to have 6,900 differences over the sequence. A nucleic acid with 99% identity would be permitted to have 690 differences over the sequence.

Next, the guidelines direct a review of the application to understand **how the application provides support for the claimed invention**.

The specification teaches a single molecule within the scope of the claimed invention, that is SEQ ID NO: 7212. The specification does not teach any variants of SEQ ID NO: 7212, nor does the specification teach any single nucleotide polymorphism within SEQ ID NO: 7212. Thus, the single molecule provided in the specification represents only one species within the vast genus claimed.

Considering then, the scope of the claims and the teachings of the specification, the guidelines direct one to **determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention as a whole** at the time the application was filed. The guidelines direct that such possession may be shown in many ways, including an actual reduction to practice, detailed drawings or in chemical formulas, and description of sufficient, relevant, identifying characteristics. In addition, for a claim drawn to a genus the requirement may be satisfied by description of a representative number of species, reduction to drawings, or by disclosure of other sufficient, relevant, identifying characteristics.

The instant specification does not provide sufficient written description to inform one of possession of the invention as a whole. There is actual reduction to practice of only a single embodiment within claims 8-11. Reduction to practice of only a single embodiment is not reduction to practice of the entire scope of the claim, and thus, applicant has not met the written description requirement by reduction to practice.

The only structural chemical formula given in the specification is SEQ ID NO: 7212. For all of the rejected claims, only a partial structure representing the entire genus is given, that is SEQ ID NO: 7212. The teachings of the specification do not couple this structure with any additional physical or chemical characteristics or functional characteristics. This structural formula represents only a single species of the claimed invention for claims 8-11. As noted in this rejection, however, the claimed invention is quite broad in nature, and this single example is not a “representative

number of species" since the entire genus of molecules encompassed within this genus is so broad and includes molecules of any possible function.

The level of skill in the art is quite high, but the unpredictability regarding the functioning of nucleic acid sequences upon modification is even higher. The function of a nucleic acid, with regard to a coding or non-coding function is highly sequence dependent. For example, the art teaches repeatedly that mutations in a critical region of a promoter element can destroy the ability of a construct to function in promotion. For example, Pietrzkowski *et al.* (Experimental Cell Research, 193, 283-290 (1991)) teaches that when synthetic promoters were produced wherein the sequence of an enhancer element was mutated, little to no promotion was observed from the constructs where the promoter was mutated (see for example Figure 6). Chan *et al.* (Plant Molecular Biology 46 :131-141, (2001)) teach that mutation in a critical XXIII element of the GAPB promoter abolished transcription completely (Figure 6), while mutations in other elements did not abolish activity (Figure 6). Thus, it is evident that it is highly unpredictable how promoter elements will respond to even very minor sequences changes. In addition, the order that promoter elements occur in a construct has an effect on the functionality of the promoter. Omilli *et al.* (Molecular and Cellular Biology, June 1986, p. 1875-1885) teach that the relative arrangement of promoter elements is a critical factor contributing to the activity of the promoter (ABSTRACT, for example). In this case, there is no functional requirement given regarding the claimed nucleic acids, and thus the claimed nucleic acids encompass a wide variety of structurally distinct

molecules whose function may or may not be associated with SEQ ID NO: 7212 in the same manner.

Thus, having carefully considered all of these factors, it is concluded that the specification does not provide adequate written description for the claimed invention.

Response to Arguments

The response filed December 10, 2007 traverses the written description rejection. It is argued that the specification demonstrates that Appellant was in possession of the claimed genus of nucleic acid molecules. This argument was thoroughly reviewed but was not found persuasive. With regard to claims 8-12, the claims further encompass sequences having 90% to less than 100% identity with SEQ ID NO: 7212 and sequences comprising these variant sequences. Thereby, the claims encompass mutants, allelic variants, splice variants and homologues of SEQ ID NO: 7212 which are not adequately described in the present specification.

Appellants state that the application describes more than just the nucleotide sequence of SEQ ID NO: 7212. It is asserted that the specification describes vectors comprising the claimed nucleic acid molecules, the addition of other nucleotides or detectable labels, fusion peptides, as well as sequences having particular sequence identity to claimed nucleic acid molecules. Appellants cite Enzo Biochem (Fed. Cir. 2002) as stating that the written inquiry is a factual one determined on a case-by-case basis and that, in a given disclosure, “it may well be that various subsequences, mutations, mixtures of those sequences are also described to one of skill in the art.”

These arguments have been fully considered but are not persuasive. The genus of nucleic acids encompassed by the claims is extremely broad and is not limited to vectors comprising the nucleic acids or to nucleic acids comprising a label. The claims further encompass mutants, allelic variants, splice variants and homologues of SEQ ID NO: 7212. A general statement in the specification of a desire to obtain gene sequences, homologues from other species, mutated species, SNPs, polymorphic sequences, promoter sequences and exogenous sequences is not equivalent to providing a clear and complete description of specific sequences which fall within the claimed genus of nucleic acids. As discussed in the rejection, the court in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), held that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". While Appellants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. In the present situation, Appellants have provided only a disclosure of a wish to obtain homologues, mutant, allelic, and splice variants of SEQ ID NO: 7212. The specification does not disclose any specific mutant, allelic, or splice variants or homologues of SEQ ID NO: 7212. Further, the functional activity of such variants is not disclosed. Accordingly, the specification has not disclosed a representative number of nucleic acid molecules within the claimed genus.

Appellants assert that they have disclosed the common structural features of the claimed nucleic acids, i.e., SEQ ID NO: 7212. However, the claims are not limited to nucleic acids which share this common structural feature. Rather, the claims encompass nucleic acids having 90-99.9% identity with SEQ ID NO: 7212. Thereby, the claimed genus of nucleic acids do not share the same common structural feature of containing the sequence of SEQ ID NO: 7212. Appellants have not disclosed what specific sequence information must be shared by the claimed genus of nucleic acid molecules in order to ascertain which nucleic acids share a common structural feature. The genus of molecules having 95-99.9% identity with SEQ ID NO: 7212 includes individual species of nucleic acids which may vary from SEQ ID NO: 7212 at any given nucleotide position within SEQ ID NO: 7212. When the individual species within the genus are compared to one another, together this genus comprises nucleic acids which vary at each and every nucleotide position within SEQ ID NO: 7212. Accordingly, the genus of nucleic acids are not considered to share a common structural feature – i.e., there is no specific structural property that is common to all members of the claimed genus if each of the individual nucleotides may be varied. Further, the claims do not recite a functional requirement for any of the claimed nucleic acids and thereby encompass nucleic acids having distinct functional properties.

At page 17, Appellants state that "closely related nucleic acid molecules falling within the scope of the invention are readily identifiable – they either contain the nucleic acid sequence of SEQ ID NO: 7212 or share a claimed identity with SEQ ID NO: 7212, or they do not. The fact that the nucleic acid molecules may comprise additional

sequences or variations is beside the point. Such modifications are readily envisioned by one of ordinary skill in the art and disclosed throughout the specification. Thus, contrary to the Examiner's analysis, claims, 8-11 are supported by an adequate written description." These arguments have been fully considered but are not found persuasive. It is noted that the criteria for meeting the Written Description requirement is not limited to providing a means for distinguishing between molecules which fall within the claimed genus and molecules which fall outside the claimed genus. Rather, the Written Description requirement is met by providing a showing that Appellants were, at the time the application was filed, in possession of the claimed invention. Providing a statement that the invention covers nucleic acid having 90-99.9% identity with SEQ ID NO: 7212 is not equivalent to disclosing specific nucleic acids which fall within the claimed genus of nucleic acids. The specification does not disclose a single molecule within the genus of nucleic acids having 90-99.9% identity with SEQ ID NO: 7212. The specification does not describe the location or identity of nucleotides which may be varied within SEQ ID NO: 7212, and does not describe the functional activity or other biological role associated with such variants. The specification also does not disclose any specific variants of SEQ ID NO: 7212 which have a functional activity or biological role distinct from that of SEQ ID NO: 7212. Modification of a nucleic acid sequence by 1 to 10% can significantly alter the functional activity of the nucleic acid and the protein encoded thereby. The genus of nucleic acids claimed is large and variable, and potentially includes nucleic acids encoding for proteins having diverse biological functions. The specification discloses only one member of this genus, i.e., SEQ ID NO:

7212. This is not sufficient to place one of skill in the art in possession of a representative number of molecules having the varied attributes and features of species within the claimed genus. Accordingly, it is maintained that the written description requirements have not been adequately met for the broadly claimed genus of homologues, splice, mutant and polymorphic variants of SEQ ID NO:7212.

For the above reasons, it is believed that the rejections should be sustained.

Conclusion

5. Claim 1 is allowable.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
March 16, 2008